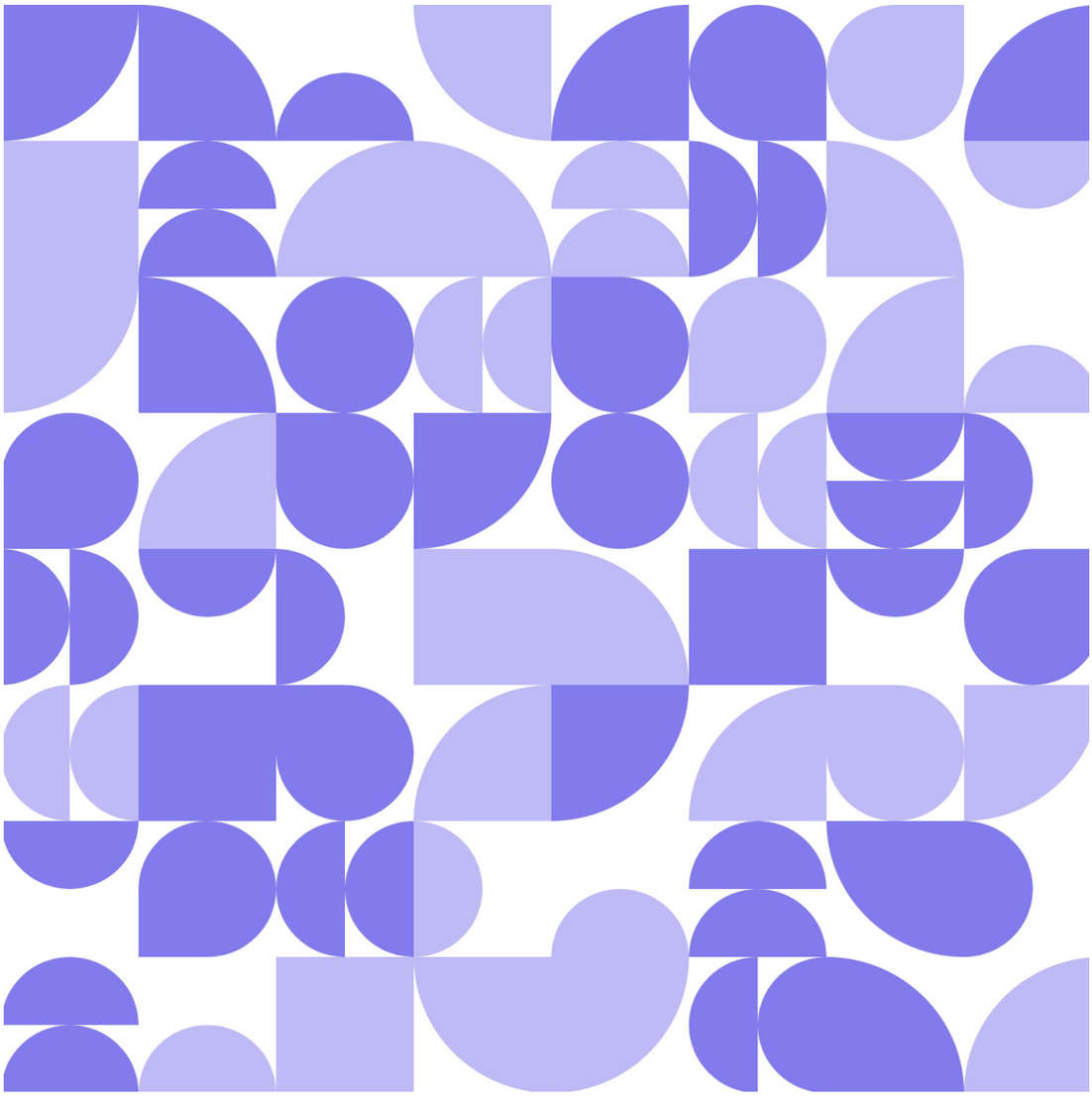

Pyrls Press — 2023

Type 2 Diabetes Pharmacotherapy

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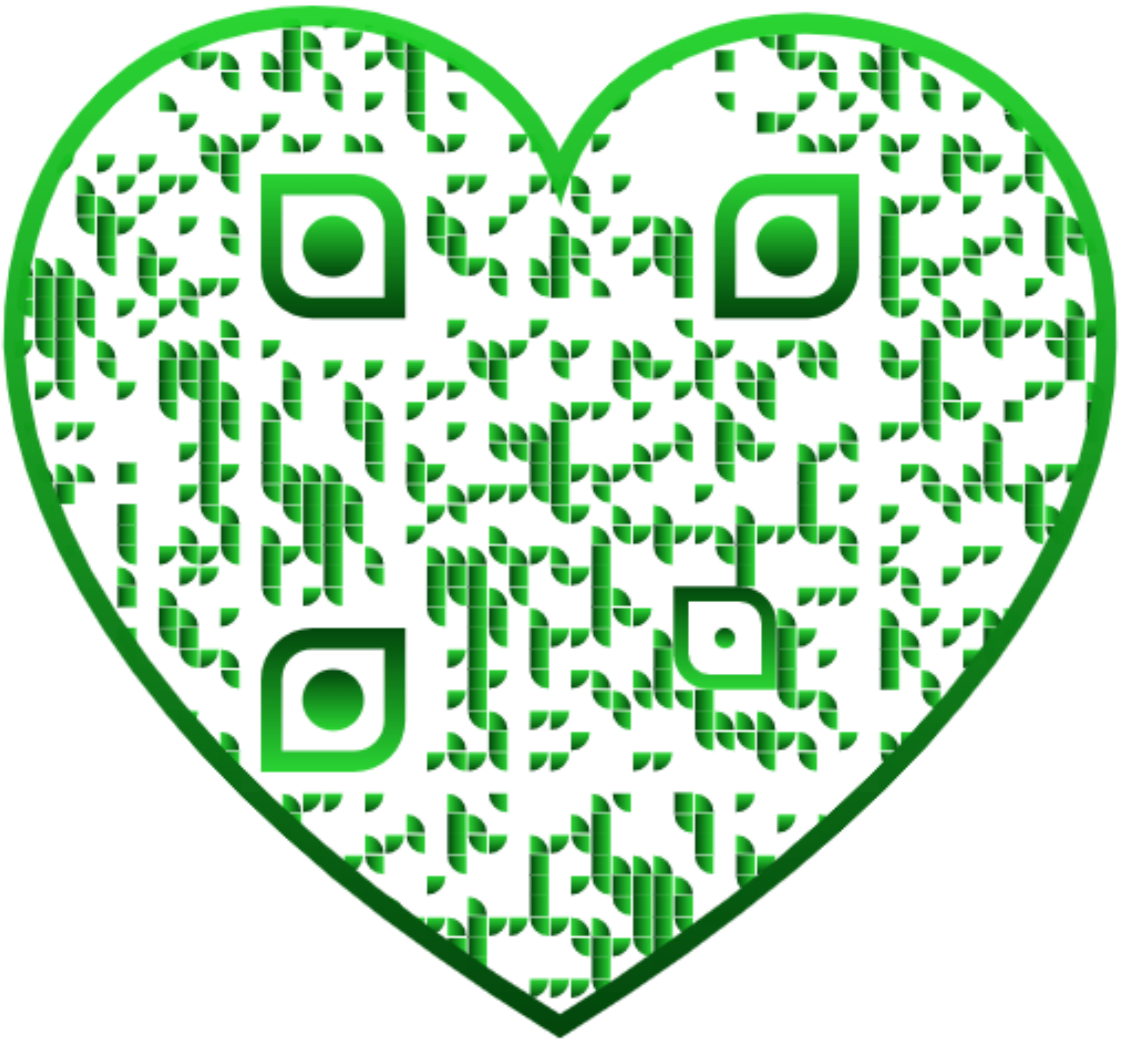

Scope of Document

This document contains a collection of concise resources on the subject of glycemic-lowering pharmacotherapy for **adult patients** with **type 2 diabetes**. It is intended to be utilized as a supplemental resource for learning and/or referencing, and is not a comprehensive guide to all relevant information on the subject.

Disclaimer

Readers should note that this document was published in **February 2023**, and the information contained in this document is **subject to frequent change.**

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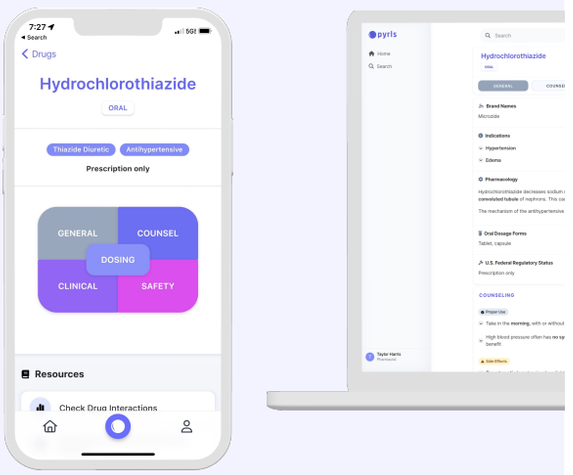

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Diagnostic Criteria and Screening for Type 2 Diabetes

Diagnostic Criteria

CONDITION	A1C (%)	FPG* (mg/dL)	2-HR PG** (mg/dL)
Diabetes	≥ 6.5	≥ 126	≥ 200
Prediabetes	5.7 - 6.4	100 - 125	140 - 199

Recreated from Table 2.2 of the ADA Standards of Care in Diabetes - 2023
*Fasting plasma glucose (FPG) should be conducted after an 8+ hour fasting period
**Plasma glucose 2 hours after the administration of 75 grams of glucose during an oral glucose tolerance test (OGTT)

Tests used to diagnose diabetes include: **hemoglobin A1C** (A1C), **fasting plasma glucose** (FPG), and **2-hour plasma glucose** (2-HR PG) during an **oral glucose tolerance test** (OGTT). These are generally considered **equally appropriate** for diagnostic screening; however, each has advantages and disadvantages.

A1C is generally **more convenient** (no fasting required) and is **less affected** by glucose fluctuations or disturbances (e.g., stress, diet changes, illness, etc.) than plasma glucose values since it is an indirect measure of average blood glucose over a period of time (~3 months).

However, A1C is **less sensitive** than plasma glucose values (FPG and 2-HR PG) and **can be unreliable**, especially when conditions affecting hemoglobin levels are present (e.g., anemias, hemodialysis, HIV, pregnancy, or other patient-specific factors). Plasma glucose value should be used when conditions affecting A1C are known or suspected. Cost and limited availability may also be disadvantages of A1C.

Plasma glucose values (FPG and 2-HR PG via OGTT) have **greater diagnostic accuracy** than A1C, especially in patients with *discordant values* (e.g., A1C value is not elevated but FPG and/or 2-hour PG values are elevated); however, can be more burdensome to prepare for and conduct, and are more subject to intermittent variability from a patient's immediate circumstances (e.g., current level stress, lifestyle, nutrition, recent illness, etc.).

A **diagnosis** for diabetes requires **two positive screening results** (from the same or separate samples). In cases of separate samples it is recommended that the second test be performed as soon as possible. In cases of **discordant results** (e.g., A1C 6.2% and FPG 175 mg/dL) the test result above the diagnostic threshold should be repeated (in this example, FPG). If the test results are near the diagnostic threshold, testing should be repeated in **3-6 months**.

Two positive tests are not required in cases where there is clear clinical evidence of diabetes, such as **hyperglycemic crisis** or random plasma glucose **≥ 200 mg/dL plus classic symptoms** of hyperglycemia (e.g. polydipsia, polyuria, blurred vision).

Diagnostic Criteria and Screening for Type 2 Diabetes

Screening for Type 2 Diabetes

In all adults not diagnosed with diabetes/prediabetes, screening should begin at age **35 years** and be repeated at least **every 3 years** (if results are normal).

Screening should be considered regardless of age for **overweight/obese*** adults with one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of cardiovascular disease
- Hypertension (BP ≥ 130/80 mmHg or on antihypertensive therapy)
- HDL < 35 mg/dL and/or triglycerides > 250 mg/dL
- Polycystic ovary syndrome
- Physical inactivity
- Clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)

**BMI ≥ 25 (or ≥ 23 in Asian American individuals)*

Patients with **prediabetes** (A1C 5.7-6.4%) should be screened **annually**. Patients with a history of **gestational diabetes** should be screened **every 3 years**.

Fasting plasma glucose, 2-hour plasma glucose following 75-gram oral glucose tolerance test or hemoglobin A1C can be used as appropriate screening methods.

Treatment Assessment and Goals

Treatment Assessment

The **primary metrics** for monitoring treatment of type 2 diabetes (T2DM) are **hemoglobin A1C** (A1C) and preprandial/postprandial glucose measurements.

In patients with diabetes, **A1C** *(or other glycemic measurement)* should be tested:

- At least **twice yearly** (e.g., every 6 months) in patients meeting their treatment goals and maintaining stable glycemic control
- At least **quarterly** (e.g., every 3 months) and as needed in patients with recent therapy change or those not meeting their glycemic goals

Other glycemic measurement includes time in range or glucose management indicator.

Preprandial and postprandial **plasma glucose levels** goals can help guide healthy diet practices, lifestyle changes, and pharmacotherapy selection and dosing.

The **primary goal of therapy** is **reducing** the patient's **plasma glucose measurements** (e.g., A1C, pre- and postprandial glucose levels) to goal *without* causing hypoglycemic episodes.

Treatment Goals

Treatment goals must be **individualized** and take into consideration comorbid conditions, hypoglycemia risk and patient-specific characteristics.

POPULATION	A1C (%)	PREPRANDIAL	1-HR PPG	2-HR PPG
Most patients*	< 7.0	80 - 130 mg/dL	- -	< 180 mg/dL
Certain patients**	< 8.0	- -	- -	- -
Pregnant***	< 6.0	< 95 mg/dL^	< 140 mg/dL	< 120 mg/dL

Recreated from Tables 6.3 and Recommendations 6.7, 15.7 and 15.8 of the ADA Standards of Care in Diabetes - 2023
*More strict goals may be reasonable if achievable without significant hypoglycemia risk
**Those at risk of or prone to severe hypoglycemia, limited life expectancy, important comorbidities, long duration of diabetes, or patients who prefer a less stringent A1C goal
***If A1C < 6% cannot be safely achieved, choosing a less strict goal of < 7% is reasonable to avoid hypoglycemic events
^Fasting plasma glucose

Deintensification of therapy for patients with A1C **between 6-7%** is **not** necessary if the hypoglycemia risk is **low**. However, if the concern for hypoglycemia is significant deintensification may be warranted as any *long-term treatment benefit* may be outweighed by the *short-term risk*.

Assessment & Modification Interval

The treatment regimen should be reassessed and modified every **3-6 months**.

Generally, patients should be assessed **every 3 months** while **not** at target glycemic goal and **every 6 months** while stable at goal. Treatment intensification for patients not at goal should not be delayed when possible.

Estimated Average Glucose

The table below provides **estimated average glucose levels** (eAG) for specific A1C values. This data can be used to *counsel patients* and *guide therapy*.

Patients are generally able to understand **blood glucose values** better than A1C. By discussing treatment goals with patients in terms of a target eAG they can better understand their own glucose readings and overall glycemic control.

A1C (%)	AVERAGE GLUCOSE (mg/dL)
5	97 (76 - 120)
6	126 (100 - 152)
7	154 (123 - 185)
8	183 (147 - 217)
9	212 (170 - 249)
10	240 (193 - 282)
11	269 (217 - 314)
12	298 (240 - 347)

Recreated from Table 6.1 from the ADA Standards of Care in Diabetes - 2023

For example, if a patient's current A1C is **9.0%** their eAG would be **212 mg/dL**. Typically, an A1C goal of **< 7.0%** is appropriate for most patients (eAG < 154 mg/dL).

Encouraging the patient to achieve an **average glucose** of < 154 mg/dL can better enable them to track their own progress between office visits and A1C tests and more clearly see the benefits of positive lifestyle modifications (e.g., dietary changes, increased physical activity, weight loss).

Overview of Hemoglobin A1C

Hemoglobin A1C Review

Before discussing the hemoglobin A1C (A1C) lab value itself, it is important to understand the relationship between A1C and **hemoglobin**. Hemoglobin is an iron-containing transport protein found in red blood cells. Over the lifespan of red blood cells (~120 days) the hemoglobin protein becomes **glycated** (chemically linked to sugar). The **greater** the concentration of glucose in the bloodstream, the **greater** amount of hemoglobin becomes glycated. The **A1C test** is a measurement of the **percentage** of glycated hemoglobin in the bloodstream.

Limitations of Hemoglobin A1C

It is important to note that hemoglobin A1C (A1C) is an **indirect measure** of a patient's **average** blood glucose levels. It does **not** provide information regarding glycemic **variability** (i.e., the frequency of hyper- and hypoglycemia) which is why assessing a collection of **plasma glucose** levels in **addition** to A1C is necessary to most effectively evaluate **glycemic control**.

Additionally, hemoglobin abnormalities may **falsely** increase or decrease A1C lab values. This should be considered when the reported A1C value(s) do **not** correlate with the patient's plasma glucose levels.

Conditions that may **falsely increase** A1C include:

- Anemia (due to iron, vitamin B12 and/or folic acid deficiency)
- Severe hypertriglyceridemia (> 1,750 mg/dL)
- Chronic alcohol consumption

Conditions that may **falsely decrease** A1C include:

- Acute or chronic blood loss
- Hemolytic anemia (e.g., sickle cell anemia, G6PD deficiency anemia)
- End-stage renal disease
- Pregnancy (screening should be performed using oral glucose tolerance test)

If suspected, the use of **alternative** measures of average glucose levels may be warranted (e.g., fructosamine test).

Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm

Page 1

Healthy lifestyle behaviors, self-management education/support and social determinants of health should be considered in all patients.

First-line pharmacotherapy should be selected based upon patient-specific factors: glycemic management needs, cardiorenal risks, comorbidities, cost and access.

Consider **combination pharmacotherapy** at initiation if A1C ≥1.5% above target goal.

Consider **early insulin initiation** with extreme hyperglycemia:
- BG ≥300 mg/dL
- A1C >10%
- Signs of catabolism

Page 2

Reassess and modify treatment every **3-6 months**

Established/High-Risk of ASCVD, **Heart Failure**, or **Chronic Kidney Disease**? **No**

Recommended independent of baseline A1C, target A1C goal, or metformin use

ASCVD (established or high risk)

GLP-1 RA or SGLT2i with proven CVD benefit

If A1C above target

- On GLP-1 RA? Consider incorporating SGLT2i with CVD benefit *(and vice versa)*
- Consider low dose TZD *(avoid in patients with HF)*

Heart Failure (preserved or reduced EF)

SGLT2i with HF benefit
- Avoid TZDs
- Avoid saxagliptin

If A1C above target

Chronic Kidney Disease (eGFR < 60 mL/min and/or UACR ≥ 30 mg/g)

On maximally tolerated **ACEi/ARB**

SGLT2i with primary evidence for reducing CKD progression
- May be initiated with an eGFR as low as 20 mL/min
- Strongest evidence of benefit when UACR ≥ 200 mg/g
- If SGLT2i therapy is contraindicated or not tolerated, use of a **GLP-1 RA** with CVD benefit is recommended

If A1C above target

On SGLT2i? Consider incorporating GLP-1 RA *(and vice versa)*

CLASS	ASCVD	HEART FAILURE	RENAL
SGLT2is	**FDA approved CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • dapagliflozin • ertugliflozin	**FDA approved HF benefit:** • dapagliflozin • empagliflozin **Evidence for benefit:** • canagliflozin • ertugliflozin	**FDA approved renal benefit:** • canagliflozin (DKD) • dapagliflozin (CKD) **Evidence for benefit:** • empagliflozin
GLP-1 RAs & GLP-1/GIP RAs *GLP-1/GIP RA tirzepatide is under investigation for CV and renal benefit*	**FDA approved CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	**Evidence for renal benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)

NOTE: Labeled indications and evidence for individual agents are subject to frequent change and geographic variability. Last updated 12/2022.

Select therapies with **adequate efficacy** to achieve and maintain **treatment goals**.

In patients with concurrent **glycemic management** and **weight management goals**, consider therapies with **high** to **very high** glucose-lowering and weight-loss efficacy.

Glucose-Lowering Efficacy

Very High:
Dulaglutide (high-dose)
Semaglutide
Tirzepatide
Insulin
Combination therapy

High:
GLP-1 RA *(not listed above)*
Metformin
SGLT2i
Sulfonylurea
TZD

Intermediate:
DPP-4i

Weight-Loss Efficacy

Very High:
Semaglutide
Tirzepatide

High:
Dulaglutide
Liraglutide

Intermediate:
GLP-1 RA *(not listed above)*
SGLT2i

Intermediate:
DPP-4i
Metformin

Cost and Access

Add oral options available in generic form/lower cost:
- SU
- TZD*

Consider insulins that are available at lower cost:
- NPH
- Regular

Patient assistance programs may be available for certain brand name medications

*Pioglitazone is available as generical; rosiglitazone is brand only (*Avandia*)

If A1C above target

Add additional agents based on patient-specific factors including:
comorbidities, risks, glycemic management needs, convenience, cost and access

Do not combine DPP-4i, GLP-1 RA and/or tirzepatide (GLP-1/GIP RA)

References: American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023. Individual manufacturer product labels.

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Type 2 Diabetes Pharmacotherapy

Updated 2023 Treatment Algorithm

Comprehensive lifestyle changes and non-insulin agents should generally be considered prior to insulin therapy

Consider **early insulin initiation** with extreme hyperglycemia: BG ≥300 mg/dL, or A1C >10% or signs of catabolism present

See Page 1 regarding non-insulin initial pharmacotherapy use and selection

Reassess and modify treatment every **3-6 months** to avoid therapeutic inertia

Injectable therapy needed to lower A1C?

Consider **GLP-1 RA** or **GLP-1/GIP RA** in most patients prior to insulin

Titrate to **maintenance dose**

Already on **GLP-1 RA** or **GLP-1/GIP RA**?
GLP-1 RA or GLP-1/GIP RA **not appropriate**?
Or is **insulin preferred**?

Add **basal insulin analog** or **bedtime NPH** based upon patient-specific factors (e.g. cost)

START: 10 units/day or 0.1-0.2 units/kg/day

TITRATE to fasting plasma glucose (FPG) target:
- Follow an evidence-based titration algorithm, e.g. ↑ 2 units every 3 days until FPG target
- Hypoglycemia is never acceptable; titrate at a rate to minimize hypoglycemia risk
- If hypoglycemia occurs for no clear reason, ↓ dose 10-20%

Assess basal insulin dose adequacy & evaluate for overbasalization

Evaluate for clinical signs of overbasalization or need for adjunctive therapy:
- basal dose >0.5 units/kg
- ↑ bedtime-morning/post-prepprandial differential
- hypoglycemia (aware or not)
- high variability

If A1C is above target

On bedtime NPH? Consider conversion to BID NPH

One possible approach:

START:
- Total dose = 80% of current
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION: Titrate based on the individual's needs

If A1C is above target

Add prandial insulin

Usually start with one dose with the largest meal or meal with greatest PPG excursion; prandial insulin can be dosed individually or mixed with NPH as appropriate

START:
- 4 units/day or 10% of basal insulin dose
- If A1C <8%, consider ↓ basal dose by 4 units/day or by 10% of basal dose

TITRATION:
- ↑ dose 1-2 units or 10-15% twice weekly
- If hypoglycemia occurs for no clear reason, ↓ dose by 10-20%

If A1C is above target

Consider BID premix insulin

START:
- Usually unit per unit at the same total insulin dose, but may require adjustment for the individual's needs

TITRATION: Titrate based on the individual's needs

Stepwise additional prandial injections

(i.e. 1 then 2 then 3 injections)

Full basal-bolus regimen

(i.e. prandial insulin w/ meals and basal insulin)

Consider self-mixed/split insulin regimen

Can adjust NPH and short/rapid-acting insulins separately

START:
- Total NPH dose = 80% of current NPH
- 2/3 given before breakfast
- 1/3 given before dinner
- Add 4 units of short/rapid insulin to each injection or 10% of reduced NPH dose

TITRATION:
- Titrate components of the regimen based on the individual's needs

References:
American Diabetes Association. Section 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2023.,
Individual manufacturer product labels.

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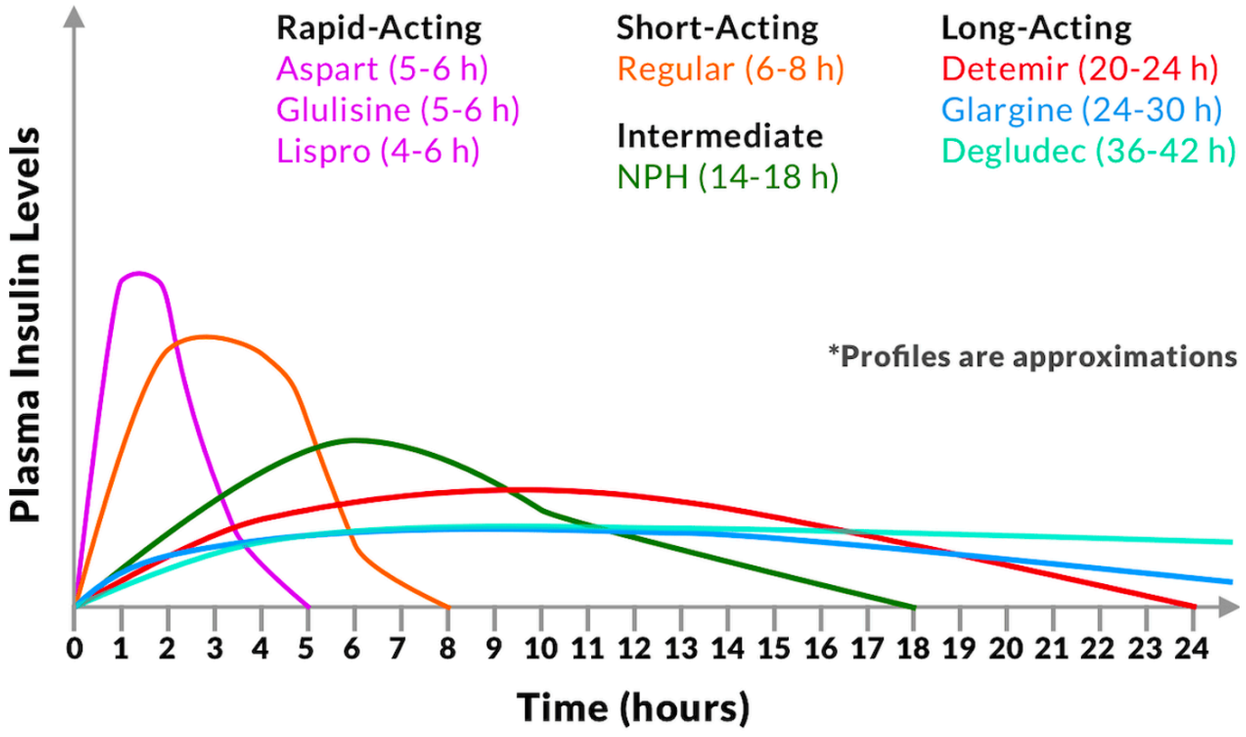
Insulin Classes and Action Profiles



Adapted and referenced from: Hirsch IB. Insulin analogues. N Engl J Med. 2005 Jan 13;352(2):174-83. https://www.ncbi.nlm.nih.gov/pubmed/15647580 and individual product labels.

BRAND	GENERIC	CLASS	DURATION	TYPE
Admelog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Afrezza	Inhaled insulin	Rapid-acting	2.5-3 hours	Human
Apidra	Insulin glulisine	Rapid-acting	5-6 hours	Analog
Basaglar	Insulin glargine	Long-acting	24-30 hours	Analog
Fiasp	Insulin aspart (faster-acting)	Rapid-acting	5-6 hours	Analog
HumaLog	Insulin lispro (conventional)	Rapid-acting	4-6 hours	Analog
Humulin N	NPH	Intermediate-acting	14-18 hours	Human
Humulin R (U-100)	Regular insulin	Short-acting	6-8 hours	Human
Humulin R (U-500)	Regular insulin	Intermediate-acting	~21 hours (13-24 hours)	Human
Lantus	Insulin glargine	Long-acting	24-30 hours	Analog
Levemir	Insulin detemir	Long-acting	20-24 hours	Analog
Lyumjev	Insulin lispro-aabc (faster-acting)	Rapid-acting	4-6 hours	Analog
NovoLog	Insulin aspart (conventional)	Rapid-acting	5-6 hours	Analog
Novolin N	NPH	Intermediate-acting	14-18 hours	Human
Novolin R	Regular insulin	Short-acting	6-8 hours	Human
Rezvoglar	Insulin glargine-aglr	Long-acting	24-30 hours	Analog
Semglee	Insulin glargine-yfgn	Long-acting	24-30 hours	Analog
Toujeo	Insulin glargine	Long-acting	24-30 hours	Analog
Tresiba	Insulin degludec	Long-acting	36-42 hours	Analog

Insulin Storage Requirements

All products are good until their expiration date when kept **unopened** and **refrigerated** (36°F-46°F [2°C-8°C]).

BRAND	GENERIC	DAYS GOOD AT ROOM TEMP (≤ 86°F [30°C])	STORAGE WHEN OPENED
Admelog SoloStar pen	Insulin lispro	28 days	**Do not refrigerate**
Admelog vial	Insulin lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Apidra SoloStar pen	Insulin glulisine	28 days (≤ 77°F [25°C])	**≤ 77°F (25°C), but do not refrigerate**
Apidra vial	Insulin glulisine	28 days (≤ 77°F [25°C])	Room or Refrigerated (≤ 77°F [25°C])
Basaglar KwikPen	Insulin glargine	28 days	**Do not refrigerate**
Fiasp FlexTouch pen	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Fiasp PenFill cartridge	Insulin aspart	28 days	**Do not refrigerate**
Fiasp vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog KwikPen	Insulin lispro	28 days	**Do not refrigerate**
Humalog vial	Insulin lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humalog Junior KwikPen	Insulin lispro	28 days	**Do not refrigerate**
Humalog TempoPen	Insulin lispro	28 days	**Do not refrigerate**
Humalog Mix 50/50 KwikPen	Insulin lispro protamine/lispro	10 days	**Do not refrigerate**
Humalog Mix 50/50 vial	Insulin lispro protamine/lispro	28 days	**Do not refrigerate**
Humalog Mix 75/25 KwikPen	Insulin lispro protamine/lispro	10 days	**Do not refrigerate**
Humalog Mix 75/25 vial	Insulin lispro protamine/lispro	28 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin N KwikPen	NPH	14 days	**Do not refrigerate**
Humulin N vial	NPH	31 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin R vial	Regular	31 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin R U-500 KwikPen	Regular	28 days	**Do not refrigerate**
Humulin R U-500 vial	Regular	40 days	Room or Refrigerated (≤ 86°F [30°C])
Humulin 70/30 KwikPen	NPH/regular	10 days	**Do not refrigerate**
Humulin 70/30 vial	NPH/regular	31 days	Room or Refrigerated (≤ 86°F [30°C])
Lantus SoloStar pen	Insulin glargine	28 days	**Do not refrigerate**
Lantus vial	Insulin glargine	28 days	Room or Refrigerated (≤ 86°F [30°C])
Levemir FlexTouch pen	Insulin detemir	42 days	**Do not refrigerate**
Levemir vial	Insulin detemir	42 days	Room or Refrigerated (≤ 86°F [30°C])
Lyumjev pen	Insulin lispro-aabc	28 days	**Do not refrigerate**
Lyumjev vial	Insulin lispro-aabc	28 days	Room or Refrigerated (≤ 86°F [30°C])

Continued on next page →

Insulin Storage Requirements *(cont.)*

All products are good until their expiration date when kept **unopened** and **refrigerated** (36°F-46°F [2°C-8°C]).

BRAND	GENERIC	DAYS GOOD AT ROOM TEMP (≤ 86°F [30°C])	STORAGE WHEN OPENED
Novolin N FlexPen	NPH	28 days	**Do not refrigerate**
Novolin N vial	NPH	42 days (≤ 77°F [25°C])	**≤ 77°F (25°C), but do not refrigerate**
Novolin R FlexPen	Regular	28 days	**Do not refrigerate**
Novolin R vial	Regular	42 days (≤ 77°F [25°C])	**≤ 77°F (25°C), but do not refrigerate**
Novolin 70/30 FlexPen	NPH/regular	28 days	**Do not refrigerate**
Novolin 70/30 vial	NPH/regular	42 days (≤ 77°F [25°C])	**≤ 77°F (25°C), but do not refrigerate**
NovoLog FlexTouch/FlexPen	Insulin aspart	28 days	**Do not refrigerate**
NovoLog vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
NovoLog PenFill cartridge	Insulin aspart	28 days	**Do not refrigerate**
NovoLog Mix 70/30 FlexPen	Insulin aspart	14 days	**Do not refrigerate**
NovoLog Mix 70/30 vial	Insulin aspart	28 days	Room or Refrigerated (≤ 86°F [30°C])
Rezvoglar KwikPen	Insulin glargine-aglr	28 days	**Do not refrigerate**
Semglee pen	Insulin glargine-yfgn	28 days	**Do not refrigerate**
Semglee vial	Insulin glargine-yfgn	28 days	Room or Refrigerated (≤ 86°F [30°C])
Toujeo SoloStar pen	Insulin glargine	56 days	**Do not refrigerate**
Toujeo Max SoloStar pen	Insulin glargine	56 days	**Do not refrigerate**
Tresiba FlexTouch pen	Insulin degludec	56 days	Room or Refrigerated (≤ 86°F [30°C])
Tresiba vial	Insulin degludec	56 days	Room or Refrigerated (≤ 86°F [30°C])

Injection Areas

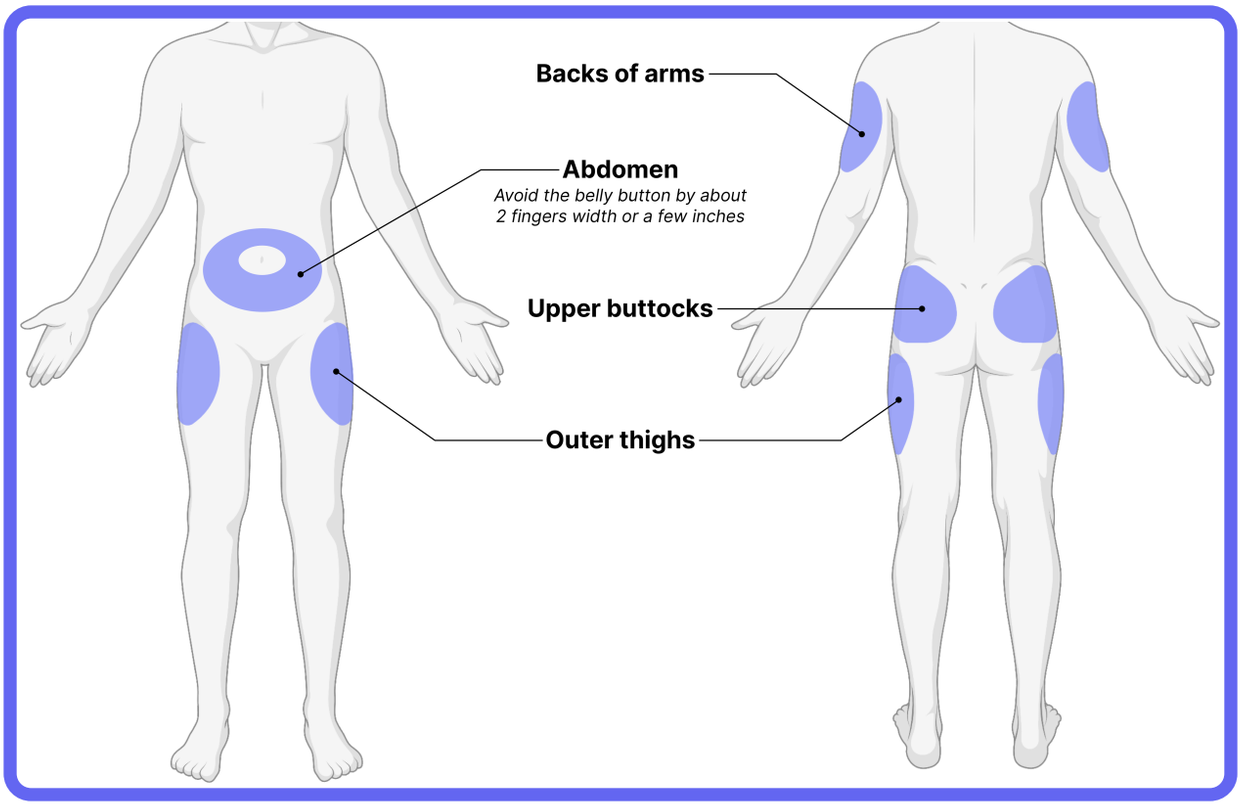
Insulin Injection Areas

Insulin is **best absorbed** when injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches); however, the outer thighs, upper buttocks and backs of arms are also acceptable injection areas.

Using the **same injection area** (e.g., abdomen) for each administration can help ensure the body receives **consistent levels** of insulin.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a **GLP-1 RA** or **GLP-1/GIP RA** with insulin, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should not be adjacent to each other.



GLP-1 RA and GLP-1/GIP RA Injection Areas

GLP-1 RAs and GLP-1/GIP RAs (e.g., tirzepatide) can be injected into the **abdomen** (staying away from the belly button by about 2 fingers width or a few inches), outer thighs and backs of arms.

Rotate injection sites (in the same general body region) to prevent **skin damage**.

If using a GLP-1 RA or GLP-1/GIP RA with **insulin**, administer at **separate injection sites** and do **not** mix the medications. The injection sites may be in the same body region but should **not** be adjacent to each other.

Type 2 Diabetes Drug Class Comparison

T2DM Drug Class	Mechanism	Route	A1C Lowering*	Hypoglycemia Risk	Weight Effect*	Cost
Biguanides (metformin)	Decreases hepatic production of glucose; increases insulin sensitivity	Oral	●●●	No	Potential for weight loss	$
SGLT2 inhibitors	Increases urinary glucose excretion	Oral	●●	No	Weight loss	$$$
GLP-1 receptor agonists	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ/Oral	●●●● **	No	Weight loss**	$$$$
GLP-1/GIP receptor agonists (e.g. tirzepatide)	Increases glucose-dependent insulin release; decreases glucagon secretion; slows gastric emptying	SQ	●●●●●	No	Weight loss	$$$$$
DPP-4 inhibitors	Increases glucose-dependent insulin release; decreases glucagon secretion	Oral	●	No	Neutral	$$$
Thiazolidinediones	Increases insulin sensitivity in muscle, fat and liver cells; increases glucose entry into cells	Oral	●●	No	+ Weight gain	$^
Sulfonylureas	Stimulates insulin secretion from pancreatic beta cells	Oral	●●●	Yes	+ Weight gain	$
Insulin Analogs	Stimulates peripheral glucose uptake by skeletal muscle and fat tissue; inhibits hepatic glucose production	SQ	●●●●● Titrate to response	Yes	+++ Weight gain	$$$
Human Insulin		SQ/Inhaled				$

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SQ = subcutaneous

*The extent of A1C lowering and weight change is highly variable based upon factors including but not limited to baseline A1C, baseline weight, patient-specific characteristics, lifestyle modifications, and whether monotherapy or a multi-drug regimen is being utilized.

**The GLP-1 receptor agonists dulaglutide and subcutaneous semaglutide have notably greater A1C-lowering efficacy and weight loss effects than other GLP-1 receptor agonists.

^Pioglitazone is generic and has low cost; however, rosiglitazone (Avandia®), which is currently unavailable in the U.S., is not available as a generic.

References: ElSayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2023. Diabetes Care 2023;46(Suppl. 1):S140–S157. Individual product manufacturer prescribing information.

Diabetes Drugs: Cardiovascular and Renal Effects

Reference(s): 3-5, 11-55, 62-63

DRUG/CLASS	ASCVD EFFECT	HF EFFECT	RENAL EFFECT	RENAL DOSING/USE*
Metformin Oral	Potential benefit	Neutral	Neutral	Contraindicated with eGFR < 30 mL/min
SGLT2is Oral	**FDA approved for CVD benefit:** • canagliflozin • empagliflozin **Neutral:** • bexagliflozin** • dapagliflozin • ertugliflozin	**FDA approved for HF benefit:** • dapagliflozin • empagliflozin **Evidence for benefit:** • canagliflozin • ertugliflozin	**FDA approved:** • canagliflozin (DKD benefit) • dapagliflozin (CKD benefit) **Evidence for benefit:** • empagliflozin **Neutral:** • ertugliflozin	Renal dose adjustments necessary
GLP-1 RAs § SUBQ injection *(except oral semaglutide)*	**FDA approved for CVD benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ) **Neutral:** • exenatide ER • lixisenatide • semaglutide (oral)	Neutral	**Evidence for benefit:** • dulaglutide • liraglutide • semaglutide (SUBQ)	Renal dose adjustments necessary for exenatide and lixisenatide Not necessary for dulaglutide, liraglutide, or semaglutide (oral and SUBQ); however, monitoring for adverse effects is warranted

* Review individual manufacturer's product labeling for specific renal dosing adjustments and considerations
** **Bexagliflozin** was FDA-approved in 2023 and has limited data suggesting neutral cardiorenal effect
§ **Tirzepatide** (GLP-1/GIP RA) is currently under investigation for cardiovascular and renal benefit

Diabetes Drugs: Cardiovascular and Renal Effects *(cont.)*

Reference(s): 3-5, 11-55

DRUG/CLASS	ASCVD EFFECT	HF EFFECT	RENAL EFFECT	RENAL DOSING/USE*
DPP-4is Oral	Neutral	**Potential risk** • saxagliptin	Neutral	Renal dose adjustments necessary for alogliptin, saxagliptin and sitagliptin Not necessary for linagliptin
TZDs Oral	**Potential CVD benefit:** • pioglitazone	**Increased risk:** • FDA boxed warning for congestive heart failure	Neutral	Renal dose adjustments not necessary Generally not recommended in renal impairment due to the potential for fluid retention
Sulfonylureas (2nd generation) Oral	Neutral	Neutral	Neutral	Glyburide: Generally not recommended in renal impairment Glimepiride, glipizide: Use lower initial dosing and titrate carefully
Insulin Analogs SUBQ injection **Human Insulin** SUBQ injection, inhaled	Neutral	Neutral	Neutral	Caution: Lower insulin doses necessary with decreased renal function Titrate according to clinical response

* Review individual manufacturer's product labeling for specific renal dosing adjustments and considerations

Metformin: Dosing and Indications

Reference(s): 3, 30-31, 61

Metformin typically reduces A1C by **1.5-2.0%** and may promote mild weight reduction.

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Metformin IR *(Glucophage)*	Improved glycemic control in T2DM	**Initial Dosing:** 500 mg PO BID with meals, OR 850 mg PO once daily with meals **Max Dosing:** 2550 mg PO daily *(in divided doses given with meals)* **Titration:** Increase dose by 500 mg *weekly* or 850 mg every *2 weeks* **as tolerated** for added glycemic control *Doses > 2000 mg daily may be given in three divided doses for improved tolerance*	eGFR 30-45 mL/min: • Initiation **not** recommended • Reassess risk-benefit of **continued** therapy eGFR < 30 mL/min: • Use is **contraindicated** • Discontinue therapy if eGFR falls below 30 mL/min Hemodialysis: • Use is **contraindicated**	Use **not** recommended in hepatic impairment due to concerns for **lactic acidosis**
Metformin ER *(Glucophage XR)*	Improved glycemic control in T2DM	**Initial Dosing:** 500 mg ER PO once daily with evening meal **Max Dosing:** 2000 mg ER daily *(with evening meal or in divided doses with meals)* **Titration:** Increase dose by 500 mg increments every week **as tolerated** for added glycemic control *If glycemic control is not achieved with 2000 mg ER once daily, consider 1000 mg ER twice daily (with meals)*	eGFR 30-45 mL/min: • Initiation **not** recommended • Reassess risk-benefit of **continued** therapy eGFR < 30 mL/min: • Use is **contraindicated** • Discontinue therapy if eGFR falls below 30 mL/min Hemodialysis: • Use is **contraindicated**	Use **not** recommended in hepatic impairment due to concerns for **lactic acidosis**

GLP-1 RAs and GLP-1/GIP RA: Efficacy and Safety

Reference(s): 3-5, 32-39, 61

GLP-1 receptor agonists typically reduce A1C by **0.7-2.1%** and can reduce body weight by 1.4-5.5 kg, depending on the individual agent and dosing utilized.
Tirzepatide (GLP-1/GIP RA) typically reduces A1C by **1.7-2.3%** and can reduce body weight by 6.3-11.2 kg, depending on the dosing utilized.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	RELATIVE GI SIDE EFFECTS
Dulaglutide *Trulicity* SUBQ injection	●●●●	**FDA approved for CVD benefit** **Evidence for renal benefit**	●●●	●●●
Exenatide *Byetta* SUBQ injection	●●	No data	●●	●
Exenatide ER *Bydureon, Bydureon BCise* SUBQ injection	●●	Neutral CVD effect	●●	●
Liraglutide^ *Victoza* SUBQ injection	●●	**FDA approved for CVD benefit** **Evidence for renal benefit**	●●●	●●
Lixisenatide *Adlyxin* SUBQ injection	●●	Neutral CVD effect	●●	●●●
Semaglutide^ *Ozempic* SUBQ injection	●●●●	**FDA approved for CVD benefit** **Evidence for renal benefit**	●●●●	●●●
Semaglutide *Rybelsus* Oral tablet	●●●	Neutral CVD effect	●●●	●●
Tirzepatide** *Mounjaro* SUBQ injection	●●●●●	*Under investigation for CVD and renal benefit*	●●●●●	●●

* The relative efficacies for A1C lowering and weight loss are based upon data from clinical trials included in the manufacturer's product labeling, post-marketing studies, and guidance from the American Diabetes Association: Standards of Care. The relative GI side effect profiles listed and ranked above are based upon information included in the manufacturer's product labeling. Actual patient A1C reduction, weight loss and side effect profile may differ in practice based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

** **Tirzepatide** is a dual GLP-1/GIP receptor agonist (all other drugs listed in the chart above are GLP-1 RA only).

^ Note that *Saxenda* (liraglutide) and *Wegovy* (semaglutide) are approved for weight-loss in patients with/without type 2 diabetes at higher than conventional dosing for glycemic control. These specific products are intentionally excluded from this chart as they fall outside the scope of the comparison.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications

Reference(s): 7, 32-39

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Dulaglutide *Trulicity* *SUBQ injection*	Improved glycemic control in T2DM Cardiovascular risk reduction *(in patients with T2DM plus established CVD or multiple risk factors)*	**Initial Dosing:** 0.75 mg once weekly **Max Dosing:** 4.5 mg once weekly **Titration:** • Increase to 1.5 mg/week for added glycemic control • If additional glycemic control is needed, increase the dosage in 1.5 mg increments after at least 4 weeks on the current dosage	No dose adjustment necessary	No dose adjustment necessary
Exenatide *Byetta* *SUBQ injection*	Improved glycemic control in T2DM	**Initial Dosing:** 5 mcg BID (within 60 minutes of meals) **Max Dosing:** 10 mcg BID **Titration:** After 1 month of therapy, may increase to 10 mcg BID for added glycemic control	CrCl < 30 mL/min: Use not recommended Dialysis: Use not recommended	Unknown, but not expected to require dose adjustments *(primarily excreted renally)*
Exenatide ER *Bydureon, Bydureon BCise* *SUBQ injection*	Improved glycemic control in T2DM	**Initial Dosing:** 2 mg ER once weekly **Max Dosing:** 2 mg ER once weekly	eGFR < 45 mL/min: Use not recommended Dialysis: Use not recommended	Unknown, but not expected to require dose adjustments *(primarily excreted renally)*

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications *(cont.)*

Reference(s): 7, 32-39

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Liraglutide *Victoza* *SUBQ injection*	Improved glycemic control in T2DM Cardiovascular risk reduction *(in patients with T2DM plus established CVD)* Note: Saxenda is a higher dose liraglutide product approved for weight loss (not included here)	**Initial Dosing:** 0.6 mg once daily for 1 week *Note - the 0.6 mg dose is not effective for glycemic control and is being used to limit GI symptoms during the initial titration* **Max Dosing:** 1.8 mg daily **Titration:** • After 1 week of 0.6 mg daily, increase to 1.2 mg daily • If additional glycemic control is required, increase to 1.8 mg daily after at least one week of treatment with 1.2 mg daily	No dose adjustment necessary	No dose adjustment necessary
Lixisenatide *Adlyxin* *SUBQ injection*	Improved glycemic control in T2DM	**Initial Dosing:** 10 mcg once daily for 14 days **Max Dosing:** 20 mcg daily **Titration:** After 14 days, increase to 20 mcg once daily	eGFR 15-30 mL/min: • Use with caution eGFR < 15 mL/min: • Use not recommended	Unknown, but not expected to require dose adjustments
Semaglutide *Ozempic* *SUBQ injection*	Improved glycemic control in T2DM Cardiovascular risk reduction *(in patients with T2DM and established CVD)* Note: Wegovy is a higher dose semaglutide product approved for weight loss (not included here)	**Initial Dosing:** 0.25 mg once weekly for 4 weeks *Note - the 0.25 mg dose is not intended for glycemic control and is being used to limit GI symptoms during the initial titration* **Max Dosing:** 2 mg once weekly **Titration:** • After 4 weeks of 0.25 mg weekly, increase to 0.5 mg weekly • If additional glycemic control is needed after at least 4 weeks of 0.5 mg weekly, the dosage may be increased to 1 mg weekly • If additional glycemic control is needed after at least 4 weeks of 1 mg weekly, the dosage may be increased to 2 mg weekly	No dose adjustment necessary	No dose adjustment necessary

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

GLP-1 RAs and GLP-1/GIP RA: Dosing and Indications *(cont.)*

Reference(s): 7, 32-39

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Semaglutide *Rybelsus* *Oral tablet*	Improved glycemic control in T2DM	**Initial Dosing:** 3 mg PO once daily for 30 days *Note - the 3 mg dose is not effective for glycemic control and is being used to limit GI symptoms during the initial titration* **Max Dosing:** 14 mg daily **Titration:** • After 30 days of 3 mg daily, increase to 7 mg daily • If additional glycemic control is needed after at least 30 days on the 7 mg dose, the dosage may be increased to 14 mg daily **Special Dosing Instructions:** Take each dose at least 30 minutes prior to first food, beverage or oral medication(s) with 4 oz of plain water	No dose adjustment necessary	No dose adjustment necessary
Tirzepatide *Mounjaro* *GLP-1/GIP RA* *SUBQ injection*	Improved glycemic control in T2DM	**Initial Dosing:** 2.5 mg once weekly for 4 weeks *Note - the 2.5 mg dose is not intended for glycemic control and is being used to limit GI symptoms during the initial titration* **Max Dosing:** 15 mg once weekly **Titration:** • After 4 weeks of 2.5 mg weekly, increase to 5 mg weekly • If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose	No dose adjustment necessary	No dose adjustment necessary

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

SGLT2 Inhibitors: Efficacy and Safety

Reference(s): 3-5, 40-44, 61-63

SGLT2 inhibitors typically reduce A1C by **0.5-1.0%** and can reduce body weight by ~3 kg.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	SAFETY CONCERNS
Bexagliflozin *Brenzavvy*	●●	*Limited data suggests neutral effect; however, additional trials are needed*	●●	• Increased urinary frequency • Volume depletion • Urinary tract infections • Genital mycotic infections • **Fournier's gangrene**
Canagliflozin *Invokana*	●●	**FDA approved for CVD benefit** **FDA approved for DKD benefit** **Evidence for HF benefit**	●●	
Dapagliflozin *Farxiga*	●●	**FDA approved for HF benefit** **FDA approved for CKD benefit** Neutral CVD effect	●●	
Empagliflozin *Jardiance*	●●	**FDA approved for CVD benefit** **FDA approved for HF benefit** **Evidence for renal benefit**	●●	
Ertugliflozin *Steglatro*	●●	Neutral CVD effect Neutral renal effect **Evidence for HF benefit**	●●	

* These relative efficacy points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight loss in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

SGLT2 Inhibitors: Dosing and Indications

Reference(s): 40-44

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Bexagliflozin *Brenzavvy*	Improved glycemic control in T2DM	**Initial Dosing:** 20 mg PO once daily in the morning **Max Dosing:** 20 mg daily	eGFR < 30 mL/min: • Not recommended Dialysis: Use is contraindicated	Mild to moderate impairment: No dose adjustment necessary Severe impairment: Has not been studied and is not recommended
Canagliflozin *Invokana*	Improved glycemic control in T2DM Cardiovascular risk reduction *(in patients with T2DM & established CVD)* Renal risk reduction *(in patients with T2DM & diabetic nephropathy)*	**Initial Dosing:** 100 mg PO once daily *(take before 1st meal of the day)* **Max Dosing:** 300 mg daily **Titration:** May increase to 300 mg daily for added glycemic control	eGFR < 60 mL/min: Limit to 100 mg daily eGFR < 30 mL/min: • Initiation not recommended • Not recommended for glycemic control • Use for renal risk reduction may continue at 100 mg daily Dialysis: Use is contraindicated	Mild to moderate impairment: No dose adjustment necessary Severe impairment: Has not been studied and is not recommended
Dapagliflozin *Farxiga*	Improved glycemic control in T2DM Heart failure risk reduction *(in patients with or without T2DM)* Renal risk reduction *(in patients with CKD with or without T2DM)*	**Initial Dosing:** • 5 mg PO once daily *(for glycemic control)* • 10 mg PO once daily *(for heart failure or renal risk reduction)* **Max Dosing:** 10 mg daily **Titration:** May increase to 10 mg daily for added glycemic control *(no titration for heart failure or renal risk reduction indications)*	eGFR < 45 mL/min: Not recommended for glycemic control eGFR < 25 mL/min: • Initiation not recommended • Use for other indications (e.g., heart failure, chronic kidney disease) may continue at 10 mg daily Dialysis: Use is contraindicated	No dose adjustment necessary However, use in severe impairment has not been studied *(use with caution)*
Empagliflozin *Jardiance*	Improved glycemic control in T2DM Cardiovascular risk reduction *(in patients with T2DM & established CVD)* Heart failure risk reduction *(in patients with or without T2DM)*	**Initial Dosing:** 10 mg PO once daily in the morning **Max Dosing:** 25 mg daily **Titration:** May increase to 25 mg daily for added glycemic control	eGFR < 30 mL/min: • Not recommended for glycemic control • Insufficient data to specify dosing for CV risk reduction eGFR < 20 mL/min: • Insufficient data to specify dosing for HF risk reduction Dialysis: Use is contraindicated	No dose adjustment necessary
Ertugliflozin *Steglatro*	Improved glycemic control in T2DM	**Initial Dosing:** 5 mg PO once daily in the morning **Max Dosing:** 15 mg daily **Titration:** May increase to 15 mg daily for added glycemic control	eGFR < 45 mL/min: Use not recommended Dialysis: Use is contraindicated	Mild to moderate impairment: No dose adjustment necessary Severe impairment: Has not been studied and is not recommended

DPP-4 Inhibitors: Efficacy and Safety

Reference(s): 3-5, 45-48, 61

DPP-4 inhibitors typically reduce A1C by **0.5-0.9%** and are weight neutral.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT LOWERING*	SAFETY CONCERNS
Alogliptin *Nesina*	●	Neutral cardiovascular effect Neutral renal effect **Evidence for heart failure risk:** • saxagliptin	Neutral effect	• Pancreatitis • Heart failure • Arthralgia
Linagliptin *Tradjenta*	●			
Saxagliptin *Onglyza*	●			
Sitagliptin *Januvia*	●			

* These relative efficacy points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight loss in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

DPP-4 Inhibitors: Dosing and Indications

Reference(s): 45-48

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Alogliptin *Nesina*	Improved glycemic control in T2DM	**Initial Dosing:** 25 mg PO once daily *(dosed renally)* **Max Dosing:** 6.25 mg to 25 mg daily *(dependent on renal function)*	CrCl 30 to < 60 mL/min: 12.5 mg once daily CrCl < 30 mL/min: 6.25 mg once daily Hemodialysis: 6.25 mg once daily *(administer without regard to timing of hemodialysis)*	Mild to moderate impairment: No dose adjustment necessary Severe impairment: Insufficient data **Pharmacokinetics Pearl:** *Alogliptin is not extensively metabolized and drug levels are not expected to be meaningfully impacted (use with caution)*
Linagliptin *Tradjenta*	Improved glycemic control in T2DM	**Initial Dosing:** 5 mg PO once daily **Max Dosing:** 5 mg daily	No dose adjustment necessary	No dose adjustment necessary
Saxagliptin *Onglyza*	Improved glycemic control in T2DM	**Initial Dosing:** 2.5 mg to 5 mg PO once daily *(dosed renally)* **Max Dosing:** 2.5 mg to 5 mg daily *(dependent on renal function)*	eGFR < 45 mL/min: 2.5 mg once daily Hemodialysis: 2.5 mg once daily *(administer after hemodialysis)*	No dose adjustment necessary
Sitagliptin *Januvia*	Improved glycemic control in T2DM	**Initial Dosing:** 100 mg PO once daily *(dosed renally)* **Max Dosing:** 25 mg to 100 mg daily *(dependent on renal function)*	eGFR 30 mL/min to <45 mL/min: 50 mg once daily eGFR < 30 mL/min: 25 mg once daily Dialysis: 25 mg once daily *(administer without regard to timing of dialysis)*	Mild to moderate impairment: No dose adjustment necessary Severe impairment: Insufficient data **Pharmacokinetics Pearl:** *Sitagliptin is not extensively metabolized and drug levels are not expected to be meaningfully impacted (use with caution)*

The combined use of **GLP-1 RAs**, **tirzepatide** (GLP-1/GIP RA) and/or **DPP-4 inhibitors** is **not recommended** due to their similar mechanism of action.

Sulfonylureas: Efficacy and Safety

Reference(s): 3-5, 48-52, 61, 64

Sulfonylureas typically reduce A1C by **1.5-2.0%** and can cause weight gain of ~1-2 kg.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE HYPOGLYCEMIA RISK*	RELATIVE WEIGHT GAIN*
Glipizide *Glucotrol,* *Glucotrol XL*		Neutral cardiovascular effect Neutral renal effect: *Use caution with renal impairment due to increased risk for hypoglycemia (particularly with the ER tablet)*	Immediate-release: Extended-release: 	
Glimepiride *Amaryl*		Neutral cardiovascular effect Neutral renal effect: *Use caution with renal impairment due to increased risk for hypoglycemia*	 *Glimepiride is a long-acting sulfonylurea and is currently listed on the Beers Criteria (use with extreme caution in elderly patients)*	
Glyburide *Diabeta,* *Glynase PresTab,* *Micronase*		Neutral cardiovascular effect Neutral renal effect: *Generally not recommended with renal impairment due to increased risk for hypoglycemia*	 *Glyburide is a long-acting sulfonylurea with renally excreted active metabolites and is currently listed on the Beers Criteria (use with extreme caution in elderly patients)*	

* These relative efficacy and risk points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight gain in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

Sulfonylureas: Dosing and Indications

Reference(s): 48-52

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Glipizide *Glucotrol*	Improved glycemic control in T2DM	**Initial Dosing:** 5 mg PO once daily 30 minutes prior to breakfast *Consider lower initial dose (2.5 mg daily) in patients at increased risk for hypoglycemia* **Max Dosing:** 40 mg daily *(daily doses > 15 mg should be divided)* **Titration:** May adjust dose in 2.5-5 mg increments for added glycemic control *(no more frequently than every several days)*	Use lower initial dosing and titrate carefully **Pharmacokinetics Pearl:** Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information **Pharmacokinetics Pearl:** Glipizide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dosing and titrate carefully **Pharmacokinetics Pearl:** As glipizide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glipizide ER *Glucotrol XL*	Improved glycemic control in T2DM	**Initial Dosing:** 5 mg ER PO once daily with breakfast (or first main meal) *Consider lower initial dose (2.5 mg ER daily) in patients at increased risk for hypoglycemia* **Max Dosing:** 20 mg ER daily **Titration:** Dose adjustments can be made according to glycemic control	Use lower initial dosing and titrate carefully **Pharmacokinetics Pearl:** Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information **Pharmacokinetics Pearl:** Glipizide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dosing and titrate carefully **Pharmacokinetics Pearl:** As glipizide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glimepiride *Amaryl*	Improved glycemic control in T2DM	**Initial Dosing:** 1-2 mg PO once daily with breakfast (or first main meal) *Consider lower initial dose (1 mg daily) in patients at increased risk for hypoglycemia* **Max Dosing:** 8 mg daily **Titration:** May adjust dose in 1-2 mg increments for added glycemic control *(no more frequently than every 1-2 weeks)*	Use lower initial dose (1 mg) in patients with renal impairment and titrate carefully **Pharmacokinetics Pearl:** Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information **Pharmacokinetics Pearl:** Glimepiride is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Dose adjustments not specified in prescribing information due to lack of adequate studies **Pharmacokinetics Pearl:** As glimepiride is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)

Sulfonylureas: Dosing and Indications *(cont.)*

Reference(s): 49-53, 60

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Glyburide *Micronase, Diabeta*	Improved glycemic control in T2DM	**Initial Dosing:** 2.5 mg to 5 mg PO once daily with breakfast (or first main meal) *Consider lower initial dose (1.25 mg daily) in patients at increased risk for hypoglycemia* **Max Dosing:** 20 mg daily *(single or divided dosing)* *Consider BID dosing when daily dose > 10 mg* **Titration:** Dosage increases should be made in increments of no more than 2.5 mg at weekly intervals according to glycemic control	Use lower initial dose (1.25 mg) in patients with renal impairment and titrate carefully **Pharmacokinetics Pearl:** Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information **Pharmacokinetics Pearl:** Glyburide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dose (1.25 mg) in patients with hepatic impairment (titrate cautiously) **Pharmacokinetics Pearl:** As glyburide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)
Glyburide, micronized *Glynase PresTab* *PresTabs are not bioequivalent to glyburide tablets*	Improved glycemic control in T2DM	**Initial Dosing:** 1.5 mg to 3 mg PO once daily with breakfast (or first main meal) *Consider lower initial dose (0.75 mg daily) in patients at increased risk for hypoglycemia* **Max Dosing:** 12 mg daily *(single or divided dosing)* *Consider BID dosing when daily dose > 6 mg* **Titration:** Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals according to glycemic control	Use lower initial dose (0.75 mg) in patients with renal impairment and titrate carefully **Pharmacokinetics Pearl:** Given that excretion is primarily via the renal route it is likely that renal dysfunction will increase duration and effect of drug (use with caution) Dialysis: Dose adjustments not specified in prescribing information **Pharmacokinetics Pearl:** Glyburide is heavily protein bound and likely not significantly affected by dialysis (use not recommended)	Use lower initial dose (0.75 mg) in patients with hepatic impairment (titrate cautiously) **Pharmacokinetics Pearl:** As glyburide is heavily protein bound and metabolism is primarily hepatic it is likely that hepatic dysfunction will increase the duration and effect of this agent (use with caution)

Thiazolidinediones: Efficacy and Safety

Reference(s): 3-5, 54-55, 61

Thiazolidinediones typically reduce A1C by **1.0-1.5%** and can cause weight gain of ~4 kg.

DRUG	RELATIVE A1C LOWERING*	CARDIORENAL EFFECTS	RELATIVE WEIGHT GAIN*	OTHER CONSIDERATIONS
Pioglitazone *Actos*	●●●	**Increased heart failure risk** **Potential cardiovascular benefit** Neutral renal effect: *Generally not recommended with renal impairment due to increased risk for fluid retention*	●●●	**Congestive heart failure risk** Risk for bladder cancer Risk for fluid retention Risk for bone fracture
Rosiglitazone *Avandia*	●●●	**Increased heart failure risk** Neutral cardiovascular effect Neutral renal effect: *Generally not recommended with renal impairment due to increased risk for fluid retention*	●●●	**Congestive heart failure risk** Increased LDL levels Risk for fluid retention Risk for bone fracture Brand only ($$$)

* These relative efficacy and risk points are based on clinical trial data involving monotherapy and combination therapy in patients with type 2 diabetes. Actual patient A1C reduction and weight gain in practice may differ based upon baseline patient characteristics, concomitant pharmacotherapy, or other factors.

Thiazolidinediones: Dosing and Indications

DRUG	INDICATIONS	DOSING	RENAL DOSING	HEPATIC DOSING
Pioglitazone *Actos*	Improved glycemic control in T2DM	**Initial Dosing:** 15 mg to 30 mg PO once daily *A lower initial dose of 15 mg recommended in patients with congestive HF (NYHA class I or II)* **Max Dosing:** 45 mg daily **Titration:** May increase dose in 15 mg increments according to glycemic control	No dose adjustment necessary *Generally not recommended with renal impairment due to increased risk for fluid retention*	No dose adjustment necessary
Rosiglitazone *Avandia*	Improved glycemic control in T2DM	**Initial Dosing:** 4 mg PO daily *(as single or two divided doses)* **Max Dosing:** 8 mg daily **Titration:** After 8-12 weeks, the dose may be increased to 8 mg daily for added glycemic control	No dose adjustment necessary *Generally not recommended with renal impairment due to increased risk for fluid retention*	Dose adjustments not specified in prescribing information: *However, rosiglitazone should not be used in patients with evidence of active liver disease or ALT levels > 2.5 times the upper limit of normal*

Drugs that Cause Hyperglycemia

CATEGORY	EXAMPLES
Atypical antipsychotics	**Most risk** Clozapine, olanzapine **Intermediate risk** Iloperidone, paliperidone, quetiapine, risperidone **Least risk** Aripiprazole, ziprasidone
Beta-blockers*^	Atenolol, metoprolol, propranolol
Systemic corticosteroids	Methylprednisolone, prednisone, prednisolone
Immunosuppressants	Cyclosporine, sirolimus, tacrolimus
Protease inhibitors	Atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Quinolones*	Ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
Thiazide-type diuretics	Chlorothiazide, chlorthalidone, hydrochlorothiazide, indapamide, metolazone

*Also known to cause hypoglycemia
^Carvedilol and nebivolol are not associated with hyperglycemia

Drugs that Cause Hypoglycemia

CATEGORY	EXAMPLES
ACE inhibitors	Benazepril, enalapril, lisinopril, ramipril, quinapril, etc.
Alcohol	Alcoholic beverages
Antiarrhythmics	Cibenzoline, disopyramide, quinidine
Quinolone antibiotics*	Ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin
Antibiotics (misc.)	Chloramphenicol, chloroquine, linezolid, pentamidine
Antidiabetics	All drugs for type 2 diabetes work to lower blood sugars; there is notable hypoglycemia risk with insulins, sulfonylureas, thiazolidinediones, and when combining multiple agents
Beta-blockers*	Nadolol, propranolol, sotalol, timolol
Anti-obesity drug	Lorcaserin
Salicylates	Aspirin, magnesium salicylate, salsalate

*Also known to cause hyperglycemia

Hypoglycemia Classification & Treatment

Symptoms of **hypoglycemia** include, but are not limited to:

- Hunger
- Irritability
- Shakiness
- Tachycardia

If allowed to progress hypoglycemia can lead to loss of consciousness. In **severe cases**, hypoglycemia may lead to seizure, coma and death.

Classification of Hypoglycemia

CATEGORY	GLYCEMIC CRITERIA/DESCRIPTION
Level 1	Glucose < 70 mg/dL and ≥ 54 mg/dL
Level 2	Glucose < 54 mg/dL
Level 3	Severe event characterized by altered mental status and/or physical status requiring assistance for treatment of hypoglycemia

Recreated from Table 6.4 of the ADA Standards of Care in Diabetes – 2023

Treatment of Hypoglycemia

The preferred treatment for hypoglycemia (glucose < 70 mg/dL) in **conscious** patients is 15-20 grams of **oral glucose** (*or any form of fast-acting carbohydrate containing glucose*). The treatment should be repeated **15 minutes later** if hypoglycemia persists.

Cognitive impairment typically occurs with Level 2 hypoglycemia (glucose < 54 mg/dL). Patients at risk for **Level 2 or 3 hypoglycemia** should be prescribed **glucagon** (available as nasal spray and injection). All caregivers should be instructed on proper use.

Counsel patients on the importance of **correcting** hypoglycemic episodes.

- The potential risks resulting from short-term *hyperglycemia* are **insignificant** compared to the clear risks and consequences of **untreated hypoglycemia**

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